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Award Number: DAMD17-97-1-7302

TITLE: A Comparison of Breast Cancer Treatment Regimens by Demographic Characteristics

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REPORT DATE: October 2000

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 074-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	October 2000	Final (5 Sep 97 - 4 Sep 00)

4. TITLE AND SUBTITLE
A Comparison of Breast Cancer Treatment Regimens by Demographic Characteristics

5. FUNDING NUMBERS
DAMD17-97-1-7302

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8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSORING / MONITORING AGENCY REPORT NUMBER

11. SUPPLEMENTARY NOTES

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution unlimited

12b. DISTRIBUTION CODE

13. ABSTRACT ***(Maximum 200 Words)***

The purpose of this study was to measure ethnic differences in treatment and survival between African American (AA) and European American (EA) women with breast cancer.

We abstracted data on cases of breast cancer diagnosed in members of an HMO in metropolitan Detroit between 1986-1996 (N=886) and followed these cases for survival through April 1997 (N=137 deaths). AA women were diagnosed at a later stage when compared with EA women. Five-year survival was 77% for AAs and 84% for EAs. The crude hazard for AAs relative to EAs was 1.6 (95% confidence interval (CI) 1.1, 2.2). Adjusting only for stage of disease at diagnosis, the hazard ratio was 1.3 (95% CI 0.9, 1.9). Adjusting only for sociodemographics (age, marital status and income), the hazard ratio was 1.2 (95% CI 0.8, 1.9). After adjusting for sociodemographics and stage, the hazard ratio was 1.0 (95% CI 0.7, 1.5). We found no material racial differences in the surgical management of breast cancer. Among women with similar medical care access, we found ethnic differences in stage of breast cancer at diagnosis. Adjusting for this difference and for income, age and marital status, eliminates the effect of race on survival.

The methods used in this study as well as the cohort of women that was assembled for this study has also lead to additional analyses contributing to the development of hypotheses that will be investigated in future studies. Preliminary results of one analysis examining ethnicity, stage of detection and mammography use show that among women age 40-49, AA ethnicity was strongly associated with later stage at diagnosis, even after adjustment for screening mammography use (adjusted odds ratio= 2.8, 95% CI 1.2-6.8). These results indicate that factors other than mammography use may explain late stage at diagnosis in the subgroup of younger (age 40-49) African American women.

14. SUBJECT TERMS
Breast Cancer

15. NUMBER OF PAGES
20

16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	Unlimited

NSN 7540-01-280-5500

Standard Form 298 (Rev. 2-89)
Prescribed by ANSI Std. Z39-18
298-102

Table of Contents

INTRODUCTION

In the United States, survival for African American women with breast cancer is inferior to that for European American women. The 1970s and 1980s marked a time of relatively stable rates of mortality among European American women with breast cancer, but increasing rates for African Americans[1]. However, the decline in mortality observed in the early 1990s for European American with breast cancer was not observed in African Americans[1,2]. Poorer survival among African Americans has been attributed to biological characteristics of the tumor, advanced stage at diagnosis, lower socioeconomic status (SES), barriers to health care, diagnostic and treatment delays[3,4] and a higher prevalence of comorbid conditions[5,6]. Although use of mammography by African American women has been reported to lag behind Caucasian women[7], recent research indicates that the racial discrepancy is narrowing[8]. However, it is too soon to see how increased use of mammography among African Americans will affect survival. The purpose of this study was to examine racial differences in breast cancer treatment and survival.

BODY

The results of our study comparing survival for African American and European American women with breast cancer were reported in detail in our annual report dated October, 1998. These results have been published in the *Journal of the National Cancer Institute*[9]. A reprint of this manuscript is included in the Appendix. We have also completed a comparison of surgical treatment for breast cancer by race. These results were published in *Surgery*[10], and a reprint is included in the appendix. The methods used in this study as well as the cohort of women that was assembled for this study has also lead to additional analyses contributing to the development of hypotheses that will be investigated in future studies. Preliminary results of one analysis examining ethnicity, stage of detection and mammography use were presented at the American Association for Cancer Research in March 2000[11]

KEY RESEARCH ACCOMPLISHMENTS

- Found that the 5-year survival for African American women was 77%, compared to 84% for European American women.
- Demonstrated that the effect of race on survival from breast cancer was eliminated after adjusting for sociodemographic characteristics and stage of disease at diagnosis.
- Observed similar patterns of surgical management of breast cancer for African American and European American women, adjusting for stage and sociodemographic characteristics.
- Preliminary results indicate that among women age 40-49, African American ethnicity was strongly associated with breast cancer stage, even after adjusting for screening mammography use. These findings may support the hypothesis that something other than mammography use (e.g. ethnic differences in breast tissue density, and therefore mammography, or ethnic differences in tumor aggressiveness) is related to stage at breast cancer diagnosis in young African American women.

REPORTABLE OUTCOMES

- Two manuscripts and one abstract published (see appendix):

  Ulcickas Yood M, Johnson CC, Blount A, Abrams J, Wolman E, McCarthy BD, Raju U, Nathanson DS, Worsham M, Wolman SR. Lack of racial differences in breast cancer survival in a managed care population. *Journal of the National Cancer Institute* 1999;1487-1491.

  Velanovich V, Ulcickas Yood M, Bawle U, Nathanson SD, Strand VF, Talpos GB, Szymanski W, Lewis FR. Racial differences in the presentation and surgical management of breast cancer. *Surgery* 1999;125:375-379.

  Johnson CC, Bawle U, Ulcickas Yood M. Ethnicity, stage of detection of breast cancer, and screening mammography in a health maintenance organization. *Proceedings of the American Association for Cancer Research* 2000;41:805-6.

CONCLUSIONS

The results of this study quantify and compare the survival of African American and European American women with breast cancer. These results indicate that in a managed care population, where access to care is equivalent, racial differences in survival are negligible after adjustment for stage, income, age and marital status. These results lend support to the view that the effect of

an intrinsic difference in tumor biology (if any) must be small and exercised mainly through its influence on stage at diagnosis.

We also studied a subset of women with breast cancer covered by HMO as well as other forms or insurance. In this population, we found no material difference in the surgical management of breast cancer after adjusting for sociodemographics and stage.

Finally, results from this study indicate that factors other than mammography use may explain late stage at diagnosis in the subgroup of younger (age 40-49) African American women.

REFERENCES

1. Chevarley F, White E: Recent trends in breast cancer mortality among White and Black US women. *Am J Public Health* 1997;87:775-781.

2. Wingo PA, Ries LAG, Rosenberg HM, Miller DS, Edwards BK: Cancer incidence and mortality, 1973-1995. *Cancer* 1998;82:1197-1207.

3. Bain RP, Greenberg RS, Whitaker JP: Racial differences in survival of women with breast cancer. *J Chron Dis* 1986;39:631-642.

4. Hunter CP, Redmond CK, Chen VW, et al: Breast cancer: factors associated with stage at diagnosis in Black and White women. *J Natl Cancer Inst* 1993;85:1129-1137.

5. West DW, Satariano WA, Ragland DR, Hiatt RA: Comorbidity and breast cancer survival: A comparison between Black and White women. *Ann Epidemiol* 1996;6:413-419.

6. Eley JW, Hill HA, Chen VW, et al: Racial differences in survival from breast cancer. *JAMA* 1994;272:947-954.

7. Burns RB, McCarthy EP, Freund KM, et al: Black women receive less mammography even with similar use of primary care. *Ann Intern Med* 1996;125:173-182.

8. Anderson LM, May DS: Has the use of cervical, breast, and colorectal cancer screening increased in the United States? *Am J Public Health* 1995;85:840-842.

9. Ulcickas Yood M, Johnson CC, Blount A, Abrams J, Wolman E, McCarthy BD, Raju U, Nathanson DS, Worsham M, Wolman SR. Lack of racial differences in breast cancer survival in a managed care population. *Journal of the National Cancer Institute* 1999;1487-1491.

10. Velanovich V, Ulcickas Yood M, Bawle U, Nathanson SD, Strand VF, Talpos GB, Szymanski W, Lewis FR. Racial differences in the presentation and surgical management of breast cancer. *Surgery* 1999;125:375-379.

11. Johnson CC, Bawle U, Ulcickas Yood M. Ethnicity, stage of detection of breast cancer, and screening mammography in a health maintenance organization. *Proceedings of the American Association for Cancer Research* 2000;41:805-6.

APPENDICES

- Two manuscripts published:

  Ulcickas Yood M, Johnson CC, Blount A, Abrams J, Wolman E, McCarthy BD, Raju U, Nathanson DS, Worsham M, Wolman SR. Lack of racial differences in breast cancer survival in a managed care population. *Journal of the National Cancer Institute* 1999;1487-1491.

  Velanovich V, Ulcickas Yood M, Bawle U, Nathanson SD, Strand VF, Talpos GB, Szymanski W, Lewis FR. Racial differences in the presentation and surgical management of breast cancer. *Surgery* 1999;125:375-379.

- Abstract Published:

  Johnson CC, Bawle U, Ulcickas Yood M. Ethnicity, stage of detection of breast cancer, and screening mammography in a health maintenance organization. *Proceedings of the American Association for Cancer Research* 2000;41:805-6.

Race and Differences in Breast Cancer Survival in a Managed Care Population

Marianne Ulcickas Yood, Christine Cole Johnson, Angela Blount, Judith Abrams, Eric Wolman, Bruce D. McCarthy, Usha Raju, David S. Nathanson, Maria Worsham, Sandra R. Wolman

Background: African-American women with breast cancer have poorer survival than European-American women. After adjustment for socioeconomic variables, survival differences diminish but do not disappear, possibly because of residual differences in health care access, biology, or behavior. This study compared breast cancer survival in African-American and European-American women with similar health care access. *Methods:* We measured survival in women with breast cancer who are served by a large medical group and a metropolitan Detroit health maintenance organization where screening, diagnosis, treatment, and follow-up are based on standard practices and mammography is a covered benefit. We abstracted data on African-American and European-American women who had been diagnosed with breast cancer from January 1986 through April 1996 (n = 886) and followed these women for survival through April 1997 (137 deaths). *Results:* African-American women were diagnosed at a later stage than were European-American women. Median follow-up was 50 months. Five-year survival was 77% for African-American and 84% for European-American women. The crude hazard ratio for African-American women relative to European-American women was 1.6 (95% confidence interval [CI] = 1.1–2.2). Adjusting only for stage, the hazard ratio was 1.3 (95% CI = 0.9–1.9). Adjusting only for sociodemographic factors (age, marital status, and income), the hazard ratio was 1.2 (95% CI = 0.8–1.9). After adjusting for age, marital status, income, and stage, the hazard ratio was 1.0 (95% CI = 0.7–1.5). *Conclusion:* Among women with similar medical care access since before their diagnoses, we found ethnic differences in stage of breast cancer at diagnosis. Adjustment for this difference and for income, age, and marital status resulted in a negligible effect of race on survival. [J Natl Cancer Inst 1999;91: 1487–91]

In the United States, survival for African-American women with breast cancer is inferior to that for European-American women *(1)*. The 1970s and 1980s marked a time of relatively stable rates of mortality among European-American women with breast cancer but of increasing rates for African-American women *(1)*. The decline in mortality observed in the early 1990s for European-American women with breast cancer was not observed in African-American women *(1,2)*. Poorer survival among African-Americans has been attributed to biologic characteristics of the tumor, advanced stage at diagnosis, lower socioeconomic status (SES), barriers to health care, diagnostic and treatment delays *(3,4)*, and a higher prevalence of comorbid conditions *(5,6)*. Although use of mammography by African-American women has been reported to lag behind use by Caucasian women *(7)*, research *(8)* indicates that this racial discrepancy is narrowing. However, it is too soon to see how increased use of mammography among African-American women will affect survival.

Most investigations *(9–11)* have found differences in tumor stage at disease presentation across ethnic groups. Use of multivariate models to control for biologic differences and sociodemographic characteristics has usually reduced but not eliminated the racial differential in survival *(6,12–15)*. Many investigators *(16–19)* have attributed the mortality differences primarily to racial disparity in SES, by way of its influence on diagnostic delays or even a lag in benefiting from medical advances *(20)*. Others *(6,9,10)* have perceived an important role for intrinsic differences in tumor aggressiveness.

We present analyses of breast cancer survival in a population of health maintenance organization (HMO) members where screening, diagnosis, treatment, and follow-up patterns are based on practice standards and are similar for all members of the population served within a large, multidisciplinary group practice. We selected this population to minimize heterogeneity in care delivery and to minimize financial barriers to health care.

Methods

Setting

The setting for this study was the Health Alliance Plan (HAP) HMO. HAP is located in southeastern Michigan and is the largest HMO in Michigan, with more than 450 000 members. Approximately 20% of these members are African-American, 53% are female, and 57% are cared for by physicians in the Henry Ford Medical Group (HFMG). Our study population was drawn from HAP members served by the HFMG. The HFMG is a large group practice that includes an urban medical center in Detroit with primary and specialty care clinics and 26 smaller clinics throughout urban and suburban southeastern Michigan.

The HFMG maintains a computerized tumor registry database accredited by the American College of Surgeons. Registry staff use a thorough case-finding system, including review of all pathology and cytology reports, as well as radiation and oncology consultations. The American Joint Commission on Cancer staging system *(21)*—called "TNM staging"—is used to determine the stage of disease by evaluating tumor size, extent of invasion, microscopic involvement of lymph nodes, and presence of metastases. HFMG registry staff link these data with Detroit area Surveillance, Epidemiology, and End Results (SEER)[1] Program records and conduct annual follow-up for vital status and recurrence. Follow-up information is complete for 94% of the women in the tumor registry.

Ascertainment of Case Patients

By use of the HFMG cancer registry, we identified all African-American and European-American women with incident breast cancer first diagnosed from January 1986 through April 1996. To minimize heterogeneity in clinical practice and access to care just before diagnosis, we limited the study population to women continuously enrolled in HAP for at least 1 year before diagnosis and assigned to a primary care physician within the HFMG at the time of diagnosis. We defined continuous enrollment as no

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See "Notes" following "References."

more than a 60-day gap in coverage according to membership files.

Outcome Data

We used several sources to identify follow-up data. First, we obtained vital status, date of death (if applicable), and date last known alive from the HFMG tumor registry. Next, for those women thought to be alive, we used HFMG administrative billing data to obtain information about hospitalizations and outpatient visits from January 1986 through April 1997. We used the billing data to update the tumor registry date where appropriate.

Identification of Related Variables

By use of the tumor registry, we obtained information on tumor characteristics, date of diagnosis, pathologic stage at diagnosis (including tumor size), and demographic factors (race, date of birth, and marital status). The demographic variables were primarily obtained from a self-administered questionnaire completed by new patients. We geocoded addresses from billing files into census block groups. We estimated household income for each woman by use of block group level median household income from the 1990 census data. Information about duration of HAP membership and mammography benefits was downloaded from the HMO membership files.

Statistical Methods

To evaluate the association between stage and race, we fit a multinomial logistic model in which we included pathologic stage (0, I, II, III, or IV) as the dependent variable and race (European-American or African-American) as the independent variable. We compared survival between African-American and European-American women by use of the hazard ratio and 95% confidence interval (CI) calculated from Cox proportional hazards models. In the model, we included marital status (unmarried or married), age at diagnosis (<55 years or ≥55 years [corresponding to the mean of this dataset]), estimated household income (<$35 000 or ≥$35 000 [likewise, the mean]), and pathologic stage (0, I, II, III, or IV) as indicator terms. Age of less than 55 years, married, income below $35 000, and stage II disease were the reference categories used in the adjusted model (because they included the largest number of women). All variables included in the model were chosen on the basis of known relationships with both breast cancer survival and race (i.e., as potential confounders). The assumption of proportional hazards was assessed graphically and by use of Schoenfeld's χ^2 goodness-of-fit procedures (22).

We considered the possibility that our method of updating the tumor registry's "date last known alive" with visit data would bias our estimates of survival if one ethnic group were more likely to have contact with the HFMG following diagnosis. Therefore, we conducted the analysis twice: First, we included only tumor registry follow-up dates; second, we used the billing data in addition. Differences between the two approaches were found to be negligible; therefore, analyses including the updated data are used in this report.

Results

We identified 1321 African-American and European-American women members of HAP who were diagnosed with breast cancer from January 1986 through April 1996 and for whom mammography was a fully covered benefit. From this group, we excluded 161 women because they were not assigned to HFMG physicians at the time of diagnosis and an additional 274 women because they were not continuously enrolled in HAP for 1 year before diagnosis, for a final sample of 886 women. The proportion of African-Americans (30%) was the same among the women excluded and the study group.

The median follow-up time was 50 months overall and was similar for African-American (49 months) and European-American (50 months) women who were alive at the end of follow-up. A total of 137 deaths occurred during the study period. Table 1 shows the baseline demographic and tumor-specific characteristics of the study population. The multinomial logistic model indicated that European-American women were more likely to have earlier stage disease at diagnosis than were African-American women. When we examined this issue more closely, European-Americans were more likely than African-Americans to have disease of an earlier stage (0 or I), with an absolute difference of 11% (95% CI = 3%–18%). Among women diagnosed with stage II disease (which includes cancers with and without lymph node involvement), we found no material difference between African-American and European-American women in the proportions with positive lymph nodes (difference = 5%; 95% CI = −6% to 17%).

The 5-year survival was 77% for African-Americans and 84% for European-Americans. The crude estimates by race are shown in Fig. 1. African-American women had poorer survival compared with European-American women (hazard ratio = 1.6; 95% CI = 1.1–2.2). Table 2 presents the hazard ratios adjusted for pathologic stage and sociodemographic factors, separately and in combination. When stage was added to the model, the hazard ratio decreased to 1.3 (95% CI = 0.9–1.9). Adjusting only for sociodemographic factors, the hazard ratio was re-

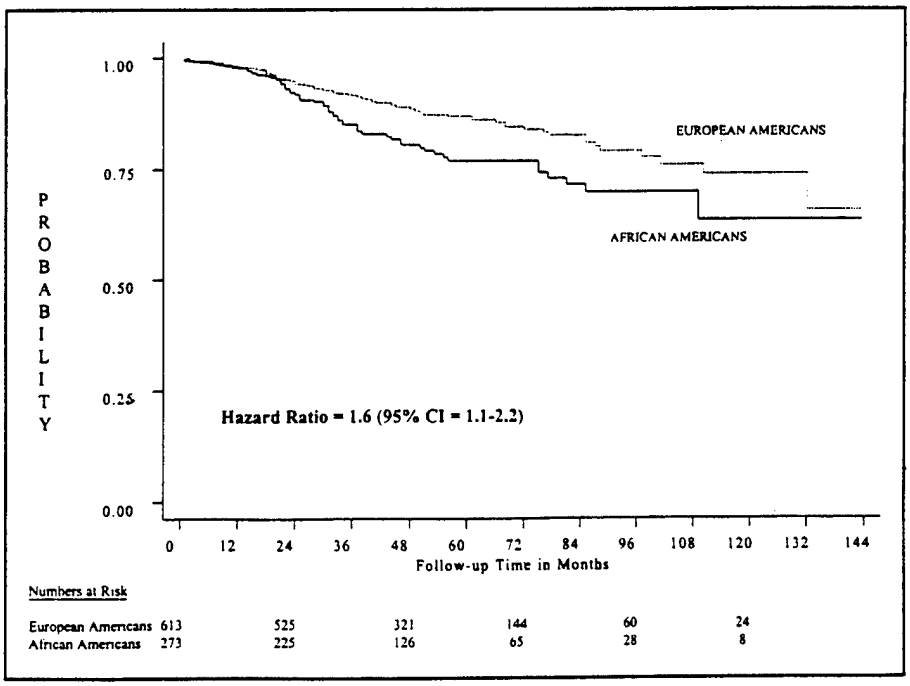

Fig. 1. Crude Kaplan–Meier survival estimates, by race. For the 886 African-American and European-American women with breast cancer who were seen at the Health Alliance Plan–Henry Ford Medical Group from January 1986 through April 1996, the cumulative survival proportion at 36 months of follow-up was 0.85 (95% confidence interval [CI] = 0.80–0.89) and 0.92 (95% CI = 0.89–0.94) for European-Americans; at 72 months, the cumulative survival was 0.77 (95% CI = 0.70–0.82) for African-Americans and 0.84 (95% CI = 0.80–0.87) for European-Americans; at 108 months, the cumulative survival was 0.70 (95% CI = 0.61–0.77) for African-Americans and 0.76 (95% CI = 0.68–0.82) for European-Americans. The table below the x-axis shows the numbers of patients at risk at representative time points. Symbols used: ------- = European-American; —— = African-American

duced to 1.2 (95% CI = 0.8–1.9). When we controlled for both stage and sociodemographics, the hazard ratio was reduced to 1.0 (95% CI = 0.7–1.5). The survival curves by race, adjusted for sociodemographic characteristics and stage, are shown in Fig. 2 and reflect this equivalent survival pattern. There was no evidence of violation of the proportional hazards assumption in the adjusted model.

Discussion

It is well-known that survival after breast cancer diagnosis is poorer for African-American women than for European-American women *(1–3,6,13–15,17,19)*. It is difficult to summarize the pertinent literature because no two studies are precisely comparable, and many papers are quoted differently by the authors who cite them. Nevertheless, some valid generalizations are relevant here. As we found, the difference in distribution of stage at detection has a major influence on differential African-American/European-American survival but does not fully explain it *(6,10–15)*.

By studying only HAP–HFMG patients, we eliminated the issue of lack of insurance coverage for screening and diagnostic services, a factor associated with both later stage at diagnosis and lower SES *(4,6,15,23)*. Even within this equal-coverage population, with its relative homogeneity of health care access and delivery, a large discrepancy in stage remains between African-American and European-American women (Table 1). Our study was not designed to investigate reasons for differences in stage at detection such as mammography use. However, two existing studies, both conducted in HAP–HFMG populations during approximately the same time period as this study, shed some light on this question. These studies measured, respectively, the proportion of women more than 50 years old who received mammography according to guidelines (relatively, 5.6% fewer African-American than European-American women) *(24)* and the proportion of women more than 50 years old with normal screening mammograms who were screened again within 2 years (relatively, 7.2% fewer African-American than European-American women) *(25)*. These small racial differences in mammography use among women in the same health care system as our sample have two implications: 1) The differences in mammography use are probably too small to explain the racial differences in stage at detection (relatively, 19% fewer African-American women with stage 0 or I disease; Tables 1 and 2) as implied above, uniform insurance coverage and clinical practices are not sufficient to equalize completely African-American and European-American women's use of breast cancer screening services.

Use of health care influences stage at diagnosis and the effectiveness of treatment *(4,11,23)*. The difficulty of obtaining data on populations with even approximate uniformity of care motivates our study. Its detailed results cannot be generalized to different populations or regions, but it constitutes an important addition to the body of work that greatly reduces the influence of race on survival by adjusting for stage and SES.

Wojcik et al. *(26)* eliminated the insurance factor by studying women cared for in the Department of Defense system, which also tries to provide equal access. The authors found that, among women with breast cancer, after adjustment for age and stage, European-American women had better survival than African-American women; however, Wojcik et al. did not control for income, a factor that varied by race in our sample of HMO members.

In our population, sociodemographic variables and stage, taken separately, had comparable confounding effects on the association between race and survival. As noted by Weiss et al. *(27)* and illustrated in the literature that we cite, SES is difficult to quantify and consists of a constellation of factors, although income plays a primary role. We know of one study besides our own that employs census data at the block group level *(28)* to improve the precision of SES estimates. Bassett and Krieger *(16)* do this by using six measures of SES other than income, and they adjust for age and stage. However, they did not study a sample with equivalent health care coverage. Both our study and that of Bassett and Krieger *(16)* come very close to eliminating race as an independent influence on survival.

The results of our study indicate that factors other than the ability to pay for services affect breast cancer survival. These factors may have some influence on stage at detection in particular. They include various beliefs about cancer risk and the usefulness of early detection, differences in the effects of various outreach and reminder strategies, differences in access mediated by transportation or the ability to get time off from work to keep appointments, obesity, comorbidities, and

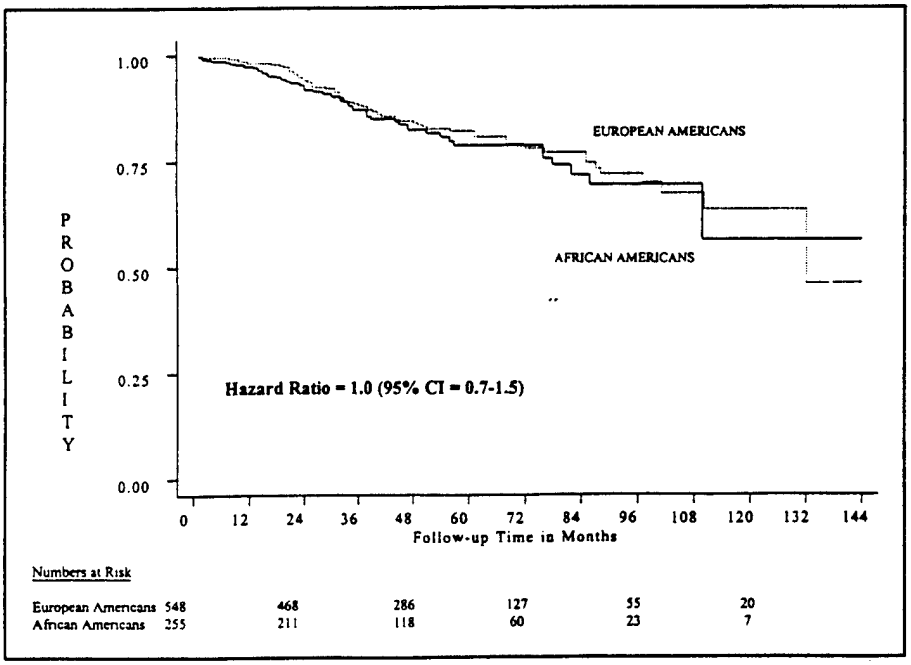

Fig. 2. Survival by race, adjusted for age, income, marital status, and stage. Adjusted Kaplan–Meier curves for 886 women with breast cancer seen at the Health Alliance Plan–Henry Ford Medical Group from January 1986 through April 1996. The table under the *x*-axis gives the numbers of patients at risk at representative time points. CI = confidence interval. Symbols used: ------- = European-American; —— = African-American.

Table 1. Baseline demographic and tumor characteristics*

	Value (95% CI)	
	African-American (n = 273)	European-American (n = 613)
Sociodemographics†		
Married	54% (48%–60%)	59% (65%–73%)
Mean age in y at diagnosis	55 (54–57)	56 (55–57)
Median household income ($1000)	26 (24–27)	44 (42–45)
Mean HMO enrollment before diagnosis, y	6.9 (6.3–7.5)	5.4 (5.1–5.7)
Tumor characteristics		
Stage‡		
0	17% (13%–22%)	21% (17%–24%)
I	29% (24%–34%)	36% (32%–40%)
II	40% (34%–46%)	33% (29%–37%)
III	9% (5%–12%)	7% (5%–12%)
IV	5% (2%–8%)	3% (1%–4%)
Mean tumor size, cm	2.4 (2.1–2.6)	2.1 (2.0–2.3)

*CI = confidence interval; HMO = health maintenance organization.

†Marital status missing for five African-American and eight European-American women. Median household income missing for 13 African-American and 56 European-American women. Both marital status and median income missing for one European-American woman.

‡Stage according to the American Joint Commission on Cancer system *(21)*.

Table 2. Effect of demographic and tumor characteristics on survival estimates

Variables in model	Hazard ratio, African-American versus European-American	95% confidence interval
Race only	1.6	1.1–2.2
Race + stage*	1.3	0.9–1.9
Race + sociodemographic factors†	1.2	0.8–1.9
Race + stage + sociodemographic factors†	1.0	0.7–1.5

*Stage according to the American Joint Commission on Cancer system *(21)*.

†Age, marital status, and median household income.

differences in breast density that modify the effectiveness of mammograms *(4,11, 23,29–33)*.

A fundamental question for us, and for the related studies we cite, is whether African-American women have intrinsically more aggressive tumors than European-American women, thus affecting their survival either directly or by way of stage at detection because of more rapid progression. Our study did not incorporate estrogen receptor status or histologic tumor grade because they were often omitted from the HFMG tumor registry and, when available, had not been evaluated consistently.

The literature can be roughly divided into studies that find intrinsic differences in tumor aggressiveness (higher nuclear and histologic grade, S-phase fraction or mitotic index, and estrogen receptor negativity) to exercise a major influence on differential African-American/European-American survival *(6,9,10)*, and the greater number that find no positive evidence for this effect because they attribute a very limited influence to race after adjustment for stage and SES *(15–20)*. In a population with uniform health care coverage, we found that the residual influence of race after adjustment is negligible (hazard ratio = 1.0; 95% CI = 0.7–1.5). This result lends support to the view that the effect of an intrinsic difference in tumor biology (if any) must be small and exercised mainly through its influence on stage at diagnosis.

References

(1) Chevarley F, White E. Recent trends in breast cancer mortality among white and black US women. Am J Public Health 1997;87:775–81.

(2) Wingo PA, Ries LA, Rosenberg HM, Miller DS, Edwards BK. Cancer incidence and mortality, 1973–1995: a report card for the U.S. Cancer 1998;82:1197–207.

(3) Bain RP, Greenberg RS, Whitaker JP. Racial differences in survival of women with breast cancer. J Chronic Dis 1986;39:631–42.

(4) Hunter CP, Redmond CK, Chen VW, Austin DF, Greenberg RS, Correa P, et al. Breast cancer: factors associated with stage at diagnosis in black and white women. Black/White Cancer Survival Study Group. J Natl Cancer Inst 1993;85:1129–37.

(5) West DW, Satariano WA, Ragland DR, Hiatt RA. Comorbidity and breast cancer survival: a comparison between black and white women. Ann Epidemiol 1996;6:413–9.

(6) Eley JW, Hill HA, Chen VW, Austin DF, Wesley MN, Muss HB, et al. Racial differences in survival from breast cancer. JAMA 1994;272: 947–54.

(7) Burns RB, McCarthy EP, Freund KM, Marwill SL, Shwartz M, Ash A, et al. Black women receive less mammography even with similar use of primary care. Ann Intern Med 1996;125: 173–82.

(8) Anderson LM, May DS. Has the use of cervical, breast, and colorectal cancer screening increased in the United States? Am J Public Health 1995;85:840–2.

(9) Chen VW, Correa P, Kurman RJ, Wu XC, Eley JW, Austin D, et al. Histological characteristics of breast carcinoma in blacks and whites. Cancer Epidemiol Biomarkers Prev 1994;3: 127–35.

(10) Elledge RM, Clark GM, Chamness GC, Osborne CK. Tumor biologic factors and breast cancer prognosis among white, Hispanic, and black women in the United States. J Natl Cancer Inst 1994;86:705–12.

(11) Moormeier J. Breast cancer in black women. Ann Intern Med 1996;124:897–905.

(12) Vernon SW, Tilley BC, Neale AV, Steinfeldt L. Ethnicity, survival, and delay in seeking treatment for symptoms of breast cancer. Cancer 1985;55:1563–71.

(13) Simon MS, Severson RK. Racial differences in survival of female breast cancer in the Detroit metropolitan area. Cancer 1996;77:308–14.

(14) Simon MS, Severson RK. Racial differences in breast cancer survival: the interaction of socioeconomic status and tumor biology. Am J Obstet Gynecol 1997;176:S233–9.

(15) Perkins P, Cooksley CD, Cox JD. Breast cancer. Is ethnicity an independent prognostic factor for survival? Cancer 1996;78: 1241–7.

(16) Bassett MT, Krieger N. Social class and black–white differences in breast cancer survival. Am J Public Health 1986;76:1400–3.

(17) Dayal HH, Power RN, Chiu C. Race and socioeconomic status in survival from breast cancer. J Chronic Dis 1982;35:675–83.

(18) Gordon NH, Crowe JP, Brumberg DJ, Berger NA. Socioeconomic factors and race in breast cancer recurrence and survival. Am J Epidemiol 1992;135:609–18.

(19) Ansell D, Whitman S, Lipton R, Cooper R. Race, income, and survival from breast cancer at two public hospitals. Cancer 1993;72: 2974–8.

(20) Heimann R, Ferguson D, Powers C, Suri D, Weichselbaum RR, Hellman S. Race and clinical outcome in breast cancer in a series with long-term follow-up evaluation. J Clin Oncol 1997;15:2329–37.

(21) American Joint Commission on Cancer. AJCC cancer staging manual. 5th ed. Philadelphia (PA): Lippincott-Raven; 1997.

(22) Schoenfeld D. Chi-squared goodness-of-fit tests for the proportional hazards regression model. Biometrika 1980;67:145–53.

(23) Lannin DR, Mathews HF, Mitchell J, Swanson MS, Swanson FH, Edwards MS. Influence of

socioeconomic and cultural factors on racial differences in late-stage presentation of breast cancer. JAMA 1998;279:1801–7.
(24) McCarthy BD, Yood MU, MacWilliam CH, Lee MJ. Screening mammography use: the importance of a population perspective. Am J Prev Med 1996;12:91–5.
(25) Yood MU, McCarthy BD, Lee NC, Jacobsen G, Johnson CC. Patterns and characteristics of repeat mammography among women 50 years and older. Cancer Epidemiol Biomarkers Prev 1999;8:595–9.
(26) Wojcik BE, Spinks MK, Optenberg SA. Breast carcinoma survival analysis for African-American and white women in an equal-access health care system. Cancer 1998;82:1310–8.
(27) Weiss LK, Severson RK, Swanson GM. Issues in comparing survival rates for Detroit and Toronto [letter]. Am J Public Health 1998;88:1556–7.
(28) Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. Am J Public Health 1992;82:703–10.
(29) Lowe JI, Barg FK, Bernstein MW. Educating African-Americans about cancer prevention and detection: a review of the literature. Soc Work Health Care 1995;21:17–36.
(30) Lacey L. Cancer prevention and early detection strategies for reaching underserved urban, low-income black women. Barriers and objectives. Cancer 1993;72(3 Suppl):1078–83.
(31) Robinson RG, Kessler LG, Naughton MD. Cancer awareness among African-Americans: a survey assessing race, social status, and occupation. J Natl Med Assoc 1991;83:491–7.
(32) Price JH, Desmond SM, Wallace M, Smith D, Stewart PW. Black Americans' perceptions of cancer. A study utilizing the Health Belief Model. J Natl Med Assoc 1988;80:1297–304.
(33) White E, Velentgas P, Mandelson MT, Lehman CD, Elmore JG, Porter P, et al. Variation in mammographic breast density by time in menstrual cycle among women aged 40–49 years. J Natl Cancer Inst 1998;90:906–10.

NOTES

[1] *Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis and the NCI makes the data available to the public for scientific research.

Supported by the Department of Defense's Breast Cancer Program (DAMRD #17-96-1-6246 and #17-97-1-7302).

Manuscript received November 23, 1998; revised June 14, 1999; accepted July 2, 1999.

Racial differences in the presentation and surgical management of breast cancer

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Background. *African American women are seen with more advanced breast cancers, are less likely to be treated with breast-conserving surgery, and generally have poorer prognoses than white women. There are a myriad of potential causes for these phenomena. The purpose of this study was to measure racial differences in the surgical treatment of breast cancer among women with comparable health care access and delivery.*

Methods. *The Breast Cancer Registry of the Department of Surgery at Henry Ford Hospital was accessed for all patients between January 1, 1990, and December 31, 1997 for whom data on race, tumor characteristics, stage, and treatment specifics were available. Socioeconomic information was collected with use of 1990 census block data. Proportions of women who received each treatment were compared for African Americans and whites with use of the relative risk (RR) and 95% confidence intervals (CI). We used multiple logistic regression to obtain estimates of the relative risk, controlling for potential confounding factors.*

Results. *Of the 1699 patients in the database, 1250 had sufficient information for analysis. A total of 8.7% of African American women were diagnosed with late-stage disease (ie, stage III or IV) compared with 7.9% of whites. Nevertheless, African American women had a lower frequency of stage I disease (30.5% vs 36.2%) and a higher frequency of stage II disease (36.8% vs 31.4%). Overall and adjusted risk estimates for age, tumor stage, marital status, median income, and type of insurance revealed no substantive or statistically significant differences between African American and white patients. The adjusted RR for local excision was 1.39 (95% CI 0.78 to 2.49), for lumpectomy and axillary dissection RR 0.92 (95% CI 0.66 to 1.29), for simple mastectomy RR 0.84 (95% CI 0.41 to 1.72), and for modified radical mastectomy RR 1.00 (95% CI 0.73 to 1.36).*

Conclusions. *In this setting of equal access to health care, African American women still have higher frequencies of stage II disease, although the frequencies for late-stage disease are similar. Nevertheless, no surgical differences were found in this population, even after the effects of socioeconomic indicators and stage at diagnosis were controlled for. Survival differences between African American and white women are unlikely to be explained by differences in treatment. (Surgery 1999;125:375-9.)*

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AFRICAN AMERICAN WOMEN WITH BREAST CANCER have been found to be first seen with more advanced disease and tend to have worse prognoses than white women, even when disease stage is controlled for.[1] Data from the National Cancer Data Base from 1995 showed that 37.5% of African Americans were first seen with stage 0 or I disease compared with 54.5% of non-Hispanic whites.[2] Attempts to explain this situation have focused on differences in tumor biologic functions,[1,3] socioeconomic conditions,[4] cultural influences,[5] and access to health care.[6] Nevertheless, 25% of the difference in survival could not be explained by stage, primary tumor characteristics, treatment, socioeconomic conditions, and demographic factors.

National data show that African American women undergo breast-conserving treatment at a lower rate compared with white women.[7,8] In the National Cancer Data Base, 49.7% of non-Hispanic whites underwent partial mastectomy compared with 46.8% of African Americans. Some of this difference was explained by level of educations and residence in a metropolitan area.[7,9]

Accepted for publication Dec 22, 1998.

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0039-6060/99/$8.00 + 0 11/56/96831

Table I. Distribution of sociodemographic characteristics by race

	African American	White
Age (y)		
≤50	129 (31.0)	263 (31.5)
51-60	88 (21.2)	213 (25.5)
61-70	107 (25.7)	188 (22.5)
>70	92 (22.1)	170 (20.4)
Marital status		
Married	176 (42.3)	539 (64.6)
Unmarried	240 (57.7)	295 (35.4)
Median income		
≤$20,000	202 (51.4)	48 (6.5)
$20,000-$35,000	122 (31.0)	182 (24.7)
$35,001-$50,000	47 (12.0)	281 (38.2)
>$50,000	22 (5.6)	225 (30.6)
Insurance		
Health Alliance Plan	189 (45.4)	381 (45.7)
Blue Cross/Blue Shield	38 (9.1)	108 (13.0)
Medicare	151 (36.3)	254 (30.5)
Other	38 (9.1)	91 (10.9)
Total	416 (100)	834 (100)

Values are number and percent.

It has been documented that low-income patients have higher frequencies of late-stage breast cancer compared with high-income groups.[2,6] Low-income groups may be underinsured, limiting their ability to obtain adequate health care. This problem with access to health care is reflected in lower rates of screening mammograms, for example.[6] This issue accounts for some of the differences seen between these groups.[10]

The hypothesis of this study is that in a managed care system with equivalent access to health care for whites and African Americans there should be no difference in stage of presentation or surgical treatment if these differences are entirely the result of factors reflecting access to health care.

MATERIAL AND METHODS

Setting. The Henry Ford Health System (HFHS) is an integrated managed care organization serving southeastern Michigan. The tertiary hospital, Henry Ford Hospital, serves not only the system's health maintenance organization (HMO) patients but also out-of-system referrals (such as fee-for-service insurers). In 1990 the Department of Surgery developed a breast cancer registry as a comprehensive database that includes information on treatments and outcomes for all breast cancer patients evaluated within the HFHS. The registry records data on age, race, tumor size, lymph node status, pathologic stage, surgical treatment, hormonal treatment, cytotoxic chemotherapy, and radiation treatment in addition to other tumor-specific data.

Identification of the study population. From the Breast Cancer Registry we identified all African American and white women seen at HFHS with newly diagnosed breast cancer between January 1, 1990, through December 31, 1997. From this group we excluded those for whom the registry had missing stage, treatment, or nodal status data.

Classification of the stages. Stages were classified in the following manner: stage 0, in situ breast ductal carcinoma (Tis); stage I, invasive ductal, lobular, tubular, or medullary carcinomas <2 cm (T1) without axillary lymph node metastasis (N0); stage II, invasive ductal, lobular, tubular, or medullary carcinomas >2 cm (T2 and T3) without lymph node metastasis (N0) or <5 cm in size without signs of direct extension to the chest wall or skin (ie, excluding T4 lesions) but with lymph node metastasis; stage III, any tumor with locally invasive lesions to chest wall or skin (T4) or tumor of any size with fixed axillary lymph nodes (N2); and stage IV, metastasis to distant organs (all M1).

Treatment and confounding data. We classified surgical treatment into 4 categories: (1) local excision, removal of mass with or without margins negative for tumor with or without adjuvant radiation therapy; (2) lumpectomy and axillary lymph node dissection, removal of mass with negative margins with axillary lymph node dissection; (3) simple mastectomy, removal of entire breast without axillary lymph node dissection; and (4) modified radical mastectomy, removal of the entire breast with axillary lymph node dissection.

Table II. Tumor characteristics of study population

	African American		*White*
Tumor stage			
0	100 (24.0)		204 (24.5)
I	127 (30.5)		302 (36.2)
II	153 (36.8)		262 (31.4)
III	31 (7.5)		61 (7.3)
IV	5 (1.2)		5 (0.6)
		$P = .18$	
Tumor size (cm)*			
≤2	35 (19.1)		92 (28.4)
2-5	110 (60.1)		171 (52.8)
>5	27 (14.8)		29 (9.0)
Extended	11 (6.0)		32 (9.9)
		$P = .014$	
Nodal status*			
0	65 (34.8)		87 (26.6)
1	111 (59.4)		229 (70.0)
2	11 (5.9)		11 (3.4)
		$P = .04$	

Values are number and percent.
*Includes only patients stages II to IV.

From the HFHS patient registration system we obtained marital status, insurance, and address. We mapped each woman's address to census block groups and estimated household income on the basis of block-group-specific 1990 census data.

Data analysis. Nominal data was analyzed with the chi-square test and randomization test as appropriate with the True Epistat[11] statistical computer program.

For each treatment category we separately calculated the proportion of African American and white women who received each treatment. We compared these proportions with use of relative risks (RR) and corresponding 95% confidence intervals (CI). We calculated the RR by dividing the proportion of African American women who received each treatment by the proportion of white women who received the treatment.

To control potential confounding, we used SAS statistical software (SAS Institute, Cary, NC) to fit a multiple logistic regression model including tumor stage (0, I, II, III, and IV); age (≤50, 51 to 60, 61 to 70, and >70 years old); marital status (married or unmarried); median income (≤$20,000, $20,001 to $35,000, $35,001 to $50,000, and >$50,000); and insurance (HMO, Blue Cross, Medicare, and other) as indicator terms. From the logistic model we obtained the odds ratio, which approximates the RR when the proportions are small, as they are in this study.

RESULTS

We identified 1699 women with newly diagnosed breast cancer from January 1, 1990, through December 31, 1997. We excluded 78 women who were not African American or white. We also excluded 180 women with missing stage information, 53 women without definitive treatment data, and 138 women with missing nodal status data, leaving a final study population of 1250 women.

The distribution of sociodemographic characteristics by race is shown in Table I. The age distribution was similar for African Americans and whites. African American women were more likely to be unmarried and had lower median household incomes compared with white women. In both groups almost half the women were members of the HFHS HMO, the Health Alliance Plan.

Table II shows the tumor characteristics of the study population. Almost 46% of African Americans were first seen with regional or distant (stage II, III, and IV) disease compared with 39% of whites ($P = .04$). Among those with stage II tumors, for which staging depends on nodal status and size, African Americans were more likely to have tumors >2 cm compared to whites (RR = 1.48, 95% CI 1.08 to 2.03), whereas African Americans were less likely to have nodal involvement than whites (RR = 0.85, 95% CI 0.71 to 1.0). Specifically, African Americans had a higher frequency of T2 and T3 tumors compared with whites ($P = .014$). But, surprisingly, they had also a higher frequency of node-negative disease ($P = .04$).

The distribution of treatments by race is shown in Table III. We found that overall and after adjustment for age, tumor stage, marital status, estimated

Table III. Distribution of treatments by race and relative risk of receiving specific treatments comparing African Americans with whites

Surgical treatment	*African American*	*White*
Conservative breast surgery		
Local excision		
Yes	80 (19.2)	156 (18.7)
No	336 (80.8)	678 (81.3)
Crude RR (95% CI)	1.03 (0.81-1.31)	1.0
Adjusted RR (95% CI)*	1.39 (0.78-2.49)	1.0
Lumpectomy and axillary dissection		
Yes	147 (35.3)	321 (38.5)
No	269 (64.7)	513 (61.5)
Crude RR (95% CI)	0.92 (0.79-1.07)	1.0
Adjusted RR (95% CI)*	0.92 (0.66-1.29)	1.0
Nonconservative breast surgery		
Simple mastectomy		
Yes	15 (3.6)	31 (3.7)
No	401 (96.4)	803 (96.3)
Crude RR (95% CI)	0.97 (0.53-1.78)	1.0
Adjusted RR (95% CI)*	0.84 (0.41-1.72)	1.0
Modified radical mastectomy		
Yes	173 (41.6)	325 (40.0)
No	243 (58.4)	509 (60.0)
Crude RR (95% CI)	1.07 (0.93-1.23)	1.0
Adjusted RR (95% CI)*	1.00 (0.73-1.36)	1.0
Total	416 (100)	834 (100)

*Adjusted for age, tumor stage, marital status, median income, and type of insurance.

household income, and insurance, African Americans and whites received similar treatments. When we dichotomized surgery as nonconserving (simple mastectomy and modified radical mastectomy) or conserving (local excision and lumpectomy with axillary dissection), we found no racial differences in treatment (adjusted RR = 0.97, 95% CI 0.72 to 1.31).

DISCUSSION

Simon and Severson[12] with use of the Surveillance, Epidemiology, and End-Results Program data for the metropolitan Detroit area (where most patients treated within the HFHS reside) found that African American women were more likely to be first seen with regional or distant disease compared with white women. The staging system used by Simon and Severson[12] is not strictly analogous to ours because some of our stage II and III patients may not have lymph node metastasis but rather large primary tumors. Nevertheless, if we define stage II, III, and IV patients as those with regional and distant disease, then the rate for African Americans in the Detroit metropolitan area derived from the data of Simon and Severson versus that of the HFHS for distant disease (44.5% vs 45.5%, respectively) and whites (36.5% vs 39.3%, respectively) are similar. This implies that stage at presentation in a managed care organization is not different than for the regional population as a whole.

Once seen for care, treatment selection is no different between African Americans and whites in our setting. Data from Muss et al[7] reported in 1992 that 14% of African American women underwent breast-conserving treatment compared with 27% of white women. In our institution from 1990 to 1997 breast conservation was achieved in >55% for both races. These data also compare favorably with the 35% breast conservation rate published by Lazovich et al[9] in 1991, who claimed that breast conservation surgery is underused. Some of these differences between our data and those of Muss et al[7] and Lazovich et al[9] could be attributed to the general increase in breast conservation after 1992. In addition, others[13,14] have shown that failure rates, cosmetic results, and treatment compliance were the same in whites and African Americans. In our managed care system all new breast cancer patients are managed by a breast surgeon, medical oncologist, and a radiation oncologist with a consensual team approach that does not distinguish between African Americans and whites.[15]

More vexing is the problem of higher-stage presentation for African Americans. Differences in

tumor biology appear to account for a small proportion of this gap.[3] Differences in mammographic screening also appear to play a limited role.[16] In a population-based study Jones et al[16] found that whites were twice as likely as African Americans to undergo screening mammography. However, after adjustment for mammography, the risk of later-stage disease in African Americans was decreased only minimally. Screening compliance in the HFHS is 73%. Patients of lower socioeconomic status are first seen with higher-stage disease and have lower stage-dependent survival.[4] On the other hand, Franzini et al[17] found in their population in Texas that after adjustment for socioeconomic status race was not a significant predictor of breast cancer mortality. Therefore, at best, survival differences can only partially be explained by poorer access to care, even when all other variables are evaluated.

Cultural differences might be implicated. Royal-Schaler et al[5] have shown that first-degree relatives of African American women with breast cancer significantly underestimate their risk for development of breast cancer and had less knowledge of the symptoms of breast disease. These authors suggested a program of systematic education to enhance African American women's understanding of breast cancer and its symptoms. Presumably, this would promote early recognition of breast cancer in this group.

In conclusion, we have demonstrated a higher rate of stage II breast cancers in African American women compared with white women but similar rates of advanced (stage III and IV) disease in a managed care environment that provides equal access to health care. However, the choice of treatment between groups is similar, implying that equal counseling to the treatment options will lead to an equal distribution of surgical treatments.

REFERENCES

1. Natarajau N, Nemoto T, Mettlin C, Murphy GP. Race-related differences in breast cancer patients: results of the 1982 national survey of breast cancer by the American College of Surgeons. Cancer 1985;56:1704-9.
2. Steele GD Jr, Jessup LM, Winchester DP, Murphy GP, Menck HR. Clinical highlights from the National Cancer Data Base: 1995. CA Cancer J Clin 1995;45:102-11.
3. Wiess SE, Tartter PI, Ahmed, et al. Ethnic differences in risk and prognostic factors for breast cancer. Cancer 1995;76:268-74.
4. Richardson JL, Langholz B, Bernstein L, et al. Stage and delay in breast cancer diagnosis by race, socioeconomic status age, and year. Br J Cancer 1992;65:922-6.
5. Royal-Schaler R, deVellis BM, Sorenson JR, et al. Breast cancer in African-American families: risk perception, cancer worry, and screening practices of first-degree relatives. Ann N Y Acad Sci 1995;768:281-5.
6. Mandeblatt J, Andrews H, Kao R, et al. Impact of access and social context on breast cancer stage at diagnosis. J Health Care Poor Underserved 1995;6:342-51.
7. Muss HB, Hunter CP, Wesley M, et al. Treatment plans for black and white women with stage II node-positive breast cancer: the National Cancer Institute Black/White Cancer Survival Study experience. Cancer 1992;70:2460-7.
8. Swanson GM, Ragheb NE, Lin CS, et al. Breast cancer among black and white women in the 1980's. Changing patterns in the United States by race, age, and extent of disease. Cancer 1993;72;788-98.
9. Lazovich D, White E, Thomas DB, Moe RE. Underutilization of breast-conserving surgery and radiation therapy among women with stage I or II breast cancer. JAMA 1991;266:3433-8.
10. Eley JW, Hill HA, Chen VW, et al. Racial differences in survival from breast cancer: results of the National Cancer Institute Black/White Cancer Survival Study. JAMA 1994;272:947-54.
11. Gustafson T. True Epistat. Richardson (TX): Sigma Services; 1991.
12. Simon MS, Severson RK. Racial differences in survival of female breast cancer in the Detroit metropolitan area. Cancer 1996;77:308-14.
13. Piece L, Fowble B, Solin LJ, et al. Conservative surgery and radiation therapy in black women with early stage breast cancer: patterns of failure and analysis of outcome. Cancer 1992;69:2831-41.
14. Smith RG, Landry JC, Hughes LL, et al. Conservative treatment of early-stage breast cancer in a medically indigent population. J Natl Med Assoc 1995;87:500-4.
15. Gabel M, Hilton NE, Nathanson SD. Multidisciplinary breast cancer clinics: do they work? Cancer 1997;79:2380-4.
16. Jones BA, Kasl SV, Curnen MG, et al. Can mammography explain the race difference in stage at diagnosis of breast cancer? Cancer 1995;75:2103-13.
17. Franzini L, Williams AF, Franklin J, Singletary SE, Theriault RL. Effects of race and socioeconomic status on survival of 1,332 black, Hispanic, and white women with breast cancer. Ann Surg Oncol 1997;42:111-8.

PhIP. In carcinogenicity experiments with rodents, PhIP induced mammary tumors. We conducted a case-control study within the cohort of the Iowa Women s Health Study to investigate the potential role of HCAs and the risk of breast cancer. A questionnaire was mailed to women in the cohort who had breast cancer diagnosed during the period from 1992 to 1994 and a random sample of cancer-free cohort members to obtain information on usual intake of meats and cooking practices. Color photographs showing various levels of doneness for hamburger, beefsteak, and bacon were included. Using an HCA database, dietary intakes of MeIQx, DiMeIQx and PhIP were estimated. Multivariate analysis was performed on data from 273 cases and 657 control subjects who completed the survey. The odds ratios (95% confidence interval) for categorical analysis of PhIP, with the 1st quintile as the referent group, were: 2nd quintile 1.1 (0.6-1.8); 3rd quintile 1.2 (0.7-1.9); 4th quintile 1.4 (0.8-2.3); and 5th quintile 1.9 (1.1-3.4), p-value for trend 0.001. There was no statistically significant increase in risk with either MeIQx or DiMeIQx. Consumption of PhIP may play an important role in the risk of breast cancer.

#5113 SULFOTRANSFERASE 1A1 (*SULT1A1*) POLYMORPHISM, ENDOGENOUS ESTROGEN EXPOSURE, WELL-DONE MEAT INTAKE, AND BREAST CANCER RISK. W Zheng, D W Xie, Z L Deng, J R Cerhan, T A Sellers, W Q Wen, and A R Folsom, *Univ of South Carolina, Columbia, SC, and University of Minnesota, Minneapolis*

Phenol sulfotransferase 1A1 (SULT1A1) is involved in the inactivation of estrogens and bioactivation of heterocyclic amines. A G→A transition at codon 213 (CGC/Arg to CAC/His) of the *SULT1A1* gene was reported recently, and individuals homozygous for the *His* allele have a substantially lower activity of this enzyme than those with other genotypes. We hypothesized that the *His* allele may be a risk factor for breast cancer, particularly among women who had risk factors related to higher endogenous estrogen exposure. This hypothesis was investigated in a case-control study conducted in a cohort of postmenopausal Iowa women who completed, in 1986, a mailed questionnaire on lifestyle factors including information on major breast cancer risk factors. DNA samples and information related to well-done meat intake were obtained from breast cancer cases diagnosed during 1992 to 1994 and a random sample of cancer-free cohort members. Multivariate analysis was performed on data from 156 cases and 332 controls who donated a blood sample. The frequency of the *His* allele was 41.6% in cases and 34.1% in controls (p = 0.02), and the risk of breast cancer was increased with the number of the *His* allele (p for trend, p = 0.02). Compared to women with the *Arg/Arg* genotype, an 80% elevated risk was observed among women homozygous for the *His* allele (95%(CI =1.0–3.2, p=0.04). This positive association was more pronounced among women who drank alcohol and had high body mass index and late age at menopause, factors related to high endogenous estrogen exposure, than those who did not have these risk factors. In contrast, the risk of breast cancer was elevated in a dose-response manner with increasing doneness level of meat intake among women with the *Arg/Arg* or *Arg/His* genotype, while this association was not evident for women with the *His/His* genotype. The results from this study suggest that homozygosity for the *SULT1A1 His*^{213} allele polymorphism may be a risk factor for breast cancer, and its effect may depend on the exposure level of endogenous estrogens and heterocyclic amines.

#5114 ASSOCIATION OF NAT2, GSTM1, GSTP1, GSTT1, FLAME-BROILED FOOD AND THE RISK OF BREAST CANCER:A NESTED CASE-CONTROL STUDY. Kala Visvanathan, Paul Strickland, Doug A Bell, Maria A Watson, Nathaniel Rothman, Sandy Hoffman, and Kathy J Helzlsouer, *Johns Hopkins Sch of Hygiene & Public Health, Baltimore, MD, National Cancer Inst, Bethesda, MD, and NIEHS, RTP, NC*

Heterocyclic amines (HCA) are pro-carcinogens that are produced when meat is cooked in direct heat for long durations. N-Acetyltransferases (NAT2) are involved in the activation of HCA. It was hypothesized that women who consumed flame-broiled foods and were rapid acetylators of NAT2 may be at increased risk of breast cancer. The association between NAT2, flame-broiled meat intake and the risk of breast cancer was assessed in a nested case-control study. Genotype information was available for 110 cases and 113 matched controls. 86% of these cases and 89% of these controls also had information on the intake of flame-broiled food in the previous month. The risk of breast cancer was increased among women who ate flame-broiled food greater than two times a month compared to those who did not (OR = 2.03 95%CI 0.88, 4.68). This risk was further increased among women who were either homozygous or heterozygous for the rapid acetylator allele of NAT2 and ate flame-broiled food (OR= 3.43 95%CI 1.14,10.35; P trend = 0.021.) Glutathione S-transferases may be involved in the detoxification of these carcinogens. Women who had the null genotype for GSTM1 or GSTT1 or who had the Ile/Val or Val/Val genotype of GSTP1 and ate flame-broiled food were also at an increased risk of breast cancer. When the four genotypes were assessed in combination, the reference group being all low risk genotypes, the risk of breast cancer increased as the burden of high risk genotypes increased only among women who ate flame-broiled food (P trend = .001). NAT2, GSTM1, GSTT1 and GSTP1 independently and in combination seemed to significantly increase the risk of breast cancer among women who ate flame-broiled food.

#5115 GLUTATHIONE *S*-TRANSFERASE P1 POLYMORPHISM IS ASSOCIATED WITH SURVIVAL AMONG WOMEN TREATED FOR BREAST CANCER. Carol Sweeney, Gail Y McClure, Manal Y Fares, Patricia A Thompson, Angie Stone, Brian F Coles, Soheila Korourian, Laura F Hutchins, Fred F Kadlubar, and Christine B Ambrosone, *M D Anderson Cancer Ctr, Houston, TX, National Ctr for Toxicological Res, Jefferson, AR, and Univ of Arkansas for Med Sci, Little Rock, AR*

Individual variability in metabolism of therapeutic agents may affect cancer treatment response and survival. Glutathione *S*-transferases (GSTs) detoxify chemotherapy agents and reactive oxidant molecules produced during radiation therapy. A GST P1 polymorphism (exon 5 A-G) results in an amino acid substitution (Ile^{105}Val) affecting catalytic efficiency of the enzyme, and may affect response to cancer therapy. We evaluated survival according to germline GST P1 genotype among women with breast cancer treated by chemotherapy or radiation therapy. DNA was extracted from normal tissue (normal lymph node or skin) from paraffin blocks from women with stage 1-4 breast cancer diagnosed 1984 to 1996. PCR and RFLP were used to detect the GST P1 exon 5 A-G substitution. Vital status was determined from cancer registry follow-up. The distribution of GST P1 genotypes among 240 cases was 46.3% Ile/Ile, 44.2% Ile/Val, and 9.6% Val/Val. GST P1 genotype was associated with survival; compared to women with Ile/Ile genotype, there was a trend (p=0.04) of better survival with increased number of GST P1 Val alleles. Hazard ratios (adjusted for stage and age) were 0.8 (95% confidence interval (CI) 0.5-1.4) for Ile/Val, and 0.3 (95% CI 0.1-1.0) for Val/Val. GST P1 genotype was not associated with age, stage at diagnosis, estrogen or progesterone receptor status, positive nodes, or menopausal status. GST P1 expression in tumor cells has been associated with poor survival and with drug resistance *in vitro*, however few studies have addressed genotype and survival. Our results indicate that women with one or two inherited alleles for the GST P1 Val variant may have better outcomes of chemotherapy or radiation treatment for breast cancer than women with GST P1 Ile/Ile.

#5116 THE GENOTYPES OF THE 5α-REDUCTASE GENE ARE RELATED WITH PSA EXPRESSION AND RISK IN SPORADIC BREAST CANCER. Andreas Scorieas, B. Bharaj, B. Hoffman, M. Giai, and E. P Diamandis, *Mount Sinai Hosp, Toronto, ON, Canada, Univ of Toronto, Toronto, ON, Canada, and Univ of Turin, Turin, Italy*

5-alpha-reductase (SRD5A2), an enzyme that is expressed in androgen dependent tissues, catalyzes the reduction of testosterone (TT) to its more bioactive form, dihydrotestosterone (DHT), which in turn transactivates a number of genes. The SRD5A2 gene harbours two frequent polymorphic sites, one in the coding region at codon 89 of exon 1, where valine is substituted by leucine (V89L) and the other in the 3′ untranslated region (3′ UTR), where a variable number of dinucleotide TA repeat lengths exists. Both polymorphisms are known to alter the activity of this enzyme. We examined 151 sporadic breast tumors from Italian patients for the V89L and TA polymorphisms by sequence and fragment analysis, respectively. Total prostatic specific antigen (PSA) concentration in all samples was measured with an ultrasensitive time-resolved immunofluorometric assay, which utilizes two monoclonal antibodies specific for PSA and has a detection limit of 0.001 ng/mL. The results showed that PSA expression was significantly elevated in tumors with VV genotype (p=0.03). LL genotype was found more frequently in younger patients (below 45 years) as well as in grade III patients (P=0.008 and P=0.037 respectively). The presence of LL alleles in breast tumors was associated with shorter disease-free (p=0.01) and overall survival (p=0.01) rates. A statistically significant association between high PSA concentrations and both TA(0)/TA(9) and TA(9) allelotypes was observed (P=0.004). These allelotypes were found rarely in patients at stage III or IV disease. Patients with TA(0)/TA(9) or TA (9) repeats, when compared to those with homozygous TA(0) allele, showed a significant reduction in the risk for relapse (p=0.04). Our results suggest that the genotype of codon 89 and the TA repeat length of the 5α-reductase gene are associated with sporadic breast cancer aggressiveness and age of onset, likely due to altered androgen metabolism.

#5117 ETHNICITY, STAGE OF DETECTION OF BREAST CANCER, AND SCREENING MAMMOGRAPHY IN A HEALTH MAINTENANCE ORGANIZATION. Christine Cole Johnson, Ulka Bawle, and Marianne Ulcickas Yood, *Bristol-Myers Squibb, Wallingford, CT, and Henry Ford Health System, Detroit, MI*

In a cohort of 886 women ascertained from an HMO and diagnosed with breast cancer from 1986-1996, crude 5 year survival for European American women (EA) was better than that for African American (AA) women (OR=1.6; 95%CI 1.1-2.2), with AA women diagnosed at a later stage. We hypothesized that the ethnic difference in stage at diagnosis could have been a result of differential use of screening mammography, although in this setting mammography is a covered benefit and strongly emphasized among the health plan physicians. To investigate this theory, we obtained information from automated data and medical records on the use of screening mammography during the three years prior to diagnosis. Only women who were continuously enrolled in the HMO during this time period were eligible. The women were classified into two age groups, 40-49 yrs. (n=141) and 50+ yrs. (n=295), based on age differences in screening guidelines. Of the 436 women in the study, 28.9% were AA. Young AA women were diagnosed with stages II-IV (65.9%) more frequently than young EA women (47.0%). This difference was much less striking among women 50+ years. In both age groups, AA women were significantly more likely than their EA counterparts

to have not received a screening mammogram (73.2% vs. 40% for younger and 61.2% vs. 31.0% for older women). However, among women 40-49, AA ethnicity was strongly associated with later stage at diagnosis even after adjustment for screening (adjusted OR=2.8; 95%CI 1.2-6.8). Our data suggest that something other than mammography use (e.g. ethnic difference in breast tissue density and therefore mammography efficacy or ethnic difference in tumor aggressiveness), is related to stage at breast cancer diagnosis in young AA women.

#5118 ADENOMATOUS POLYPS AND EPOXIDE HYDROLASE POLYMORPHISMS - RELATION TO SMOKING AND COOKED MEAT CONSUMPTION. Cornelia M Ulrich, J Bigler, J Whitton, L Fosdick, R Bostick, and J D Potter, *Fred Hutchinson Cancer Res Ctr, Seattle, WA*

Epoxide hydrolases play an important role in activation and detoxification of xenobiotics particularly polycyclic aromatic hydrocarbons (PAHs). PAHs are the product of incomplete pyrolysis of organic compounds. They can be activated to reactive metabolites that bind covalently to DNA and form bulky adducts. Some PAHs are known carcinogens. In a study of adenomatous polyps (N cases = 533; N controls = 649), we investigated the role of 2 polymorphisms in exon 3(Tyr113His) and exon 4 (His139Arg) of epoxide hydrolase 1 (EpHX 1) - and their interaction with smoking and meat intake. The age- and sex-adjusted ORs (95% CI) for exon 3 polymorphisms compared to Tyr/Tyr (ref) were Tyr/His: 1.0 (0.8–1.3) and His/His: 1.4 (0.9–2.2). The ORs for exon 4 polymorphisms were all close to 1.0.Current smoking was associated with a 2-fold increase in risk of adenomatous polyps compared to never smokers. The increased risk of colorectal adenoma associated with current smoking was more pronounced among double heterozygotes for the exon 3/ exon 4 EpHX1 polymorphisms (OR=4.9 (2.0-11.9) compared to never smokers with wildtype/wildtype). Fried, baked, or broiled meat intake of >5 servings/wk (high) compared to ≤1 serving/wk (low) was associated with a two-fold increase in risk. Although meat intake explains most of the elevated risk, compared to wildtype/low meat-intake individuals, the highest risks were seen for those with the homozygous variant genotype of exon 3 and moderate (OR=4.2 (1.4–13.0)) or high (OR=2.7 (1.1–6.8)) meat intake. Exon 4 polymorphisms did not modify the risk associated with meat consumption.

#5119 HETEROCYCLIC AMINES IN COOKING FUMES AND LUNG CANCER RISK AMONG CHINESE WOMEN IN SINGAPORE. Adeline Seow, W. T Poh, M. Teh, P. Eng, Y. T Wang, W. C Tan, M. C Yu, and H. P Lee, *National Univ of Singapore, Singapore, Singapore Gen Hosp, Singapore, Tan Tock Seng Hosp, Singapore, and Univ of Southern CA, CA*

Heterocyclic amines are known carcinogens, which have been identified in cooked meat, and also in fumes generated during frying or grilling of meats. We conducted a case-control study of 303 Chinese women with pathologically confirmed, primary carcinomas of the lung, and 765 controls to examine the association between exposure to meat cooking and lung cancer risk. Data on demographic background, smoking status and domestic cooking exposure, including stir-frying of meat, were obtained by in-person interview while in hospital. The proportion of smokers (current or ex-smokers) among cases and controls was 41.7% and 13.1% respectively. Among smokers, women who reported that they stir-fried daily in the past had a significantly increased risk of lung cancer (adjusted odds ratio (OR) 1.9, 95% CI 1.0–3.7) and among these women, risk was enhanced for those who stir-fried meat daily (OR 2.5, 95% CI 1.2–4.8). Women who stir-fried daily, but cooked meat less often than daily did not show an elevated risk (OR 1.0, 95% CI 0.4 – 2.1). Risk was further increased among women stir-frying meat daily who reported that their kitchen was filled with oily fumes during cooking (OR 3.1, 95% C.I. 1.5 – 6.4). Our results suggest that inhalation of carcinogens such as heterocyclic amines generated during frying of meat increases risk of lung cancer among smokers. Further studies in different settings are warranted to confirm these findings, which may also help to explain the higher risk observed among women smokers compared with men.

#5120 CIGARETTE COMPOSITION AS A POSSIBLE EXPLANATION OF US-JAPAN DIFFERENCES IN LUNG CANCER RATES. M V Djordjevic, S D Stellman, T Takezaki, and K Tajima, *American Health Fdn, Valhalla, NY*

US male lung cancer mortality rates greatly exceed those in Japan, despite a much higher prevalence of smoking among Japanese. To find explanations for this anomaly we measured levels of nicotine, "tar", and the carcinogens BaP and NNK in popular American and Japanese cigarettes, and carried out a case-control study in both countries using comparable designs and data collection instruments. BaP is a representative PAH which causes squamous cell lung cancer while NNK is a tobacco-specific nitrosamine which causes adenocarcinoma of the lung in rodents. We interviewed 371 cases and 373 age-matched controls in New York City and Washington, DC, and 410 cases, 252 hospital controls, and 411 age-matched healthy controls randomly selected from electoral rolls in Nagoya, Japan. The odds ratio (OR) for lung cancer in current US smokers relative to non-smokers was 39.2 [95% confidence interval (CI) = 21-71], which was ten times as high as the OR for current smokers in Japanese relative to hospital controls (OR=3.8, 95% CI = 2.0-7.1) and six times higher than in Japanese relative to community controls (OR=6.3, 95% CI = 3.7-10.9). There were no substantial differences in duration of smoking, cigarettes per day, age at onset, or inhalation between US and Japanese smokers. Yields of nicotine were similar for leading brands in both countries (≥ 1.0 mg/cig.). However, yields of "tar", BaP, and NNK were significantly higher in mainstream smoke of U.S. brands. Smoking behaviors by themselves do not appear to explain US-Japan differences in lung cancer rates, but differences in cigarette carcinogen yields may partly explain the observed differences between the two groups.

#5121 *H. PYLORI* INFECTION, SERUM MICRONUTRIENTS AND SUBSEQUENT RISK OF GASTRIC DYSPLASIA OR CANCER IN A HIGH-RISK POPULATION IN SHANDONG, CHINA. Weicheng You, L Zhang, M H Gail, Y C Chang, J F Fraumeni Jr., and G W Xu, *Beijing Institute for Cancer Res, Beijing, China, and National Cancer Inst, Bethesda, MD*

To determine the risk factors for progression of precancerous gastric lesions in Linqu County, China, an endoscopic screening survey was launched among 3,399 adults in this area in 1989-1990. Antibodies to *H. pylori* and levels of serum micronutrients were assayed for approximately 2,300 and 600 adults without gastric cancer (GC) at baseline, respectively. Data on cigarette smoking, alcohol drinking and other characteristics of the participants were obtained by interview. The cohort was subsequently followed, with endoscopic and histopathologic examinations conducted in 1994. Antibodies to *H. pylori* infection, levels of serum micronutrients and other characteristics were compared between those with progression from superficial gastritis (SG), chronic atrophic gastritis (CAG), or intestinal metaplasia (IM) to dysplasia (DYS) or GC vs. those with no change or with regression seen in 1994. Infection with *H. pylori* at baseline (OR=1.4, 95% CI, 1.0—1.9) was associated with progression to DYS/GC during the 4.5-year follow up. The risk of progression to DYS/GC increased with the number of years of smoking cigarettes and with number of cigarettes smoked. In contrast, risk of progression to DYS/GC decreased by 70% (OR=0.3, 95% CI, 0.1–0.7) among persons with 1989–1990 ascorbic acid levels in the highest tertile, as compared with those to lower levels. No such associations were observed between the progression of DYS/GC and other micronutrients including retinol, beta-carotene, alpha-tocopherol, selenium, ferritin and zinc:copper ratio. The findings suggest that *H. pylori* infection, cigarette smoking and lower levels of dietary vitamin C contribute to the progression of precancerous lesions in leading to GC in this high-risk population.

#5122 THE EPIDEMIOLOGY OF HEPATOCELLULAR CARCINOMA: INTERACTIONS BETWEEN ATOMIC-BOMB RADIATION, CIGARETTE SMOKING AND HEPATITIS B AND C INFECTIONS. Gerald B Sharp, Terumi Mizuno, John B Cologne, Shoji Tokuoka, and Kiyohiko Mabuchi, *Radiation Effects Res Fdn, Hiroshima, Japan*

We conducted a nested case-control, epidemiologic study using subjects drawn from the Life Span Study cohort of approximately 120,000 Hiroshima and Nagasaki residents, who were both exposed and non-exposed to radiation from the 1945 Atomic-bombings. A total of 307 hepatocellular carcinoma (HCC) cases and 897 autopsied controls who died from 1952-1997 were included. Controls were frequency matched to cases on age, sex, year of death, city of residence, and radiation exposure. Archival tissue samples were assessed for hepatitis B virus (HBV) status using staining and PCR. Reverse transcriptase (RT) PCR was used to determine hepatitis C virus (HCV) status. Radiation exposure estimates were based on physical calculations of yield combined with individual data about location during bombing and shielding by buildings, terrain, and body tissue; liver dose was estimated as a sum of the gamma and neutron dose with the latter multiplied by 10 because of its higher biological effectiveness. Cigarette smoking history was assessed using interviews and mail surveys. Adjusting for confounders, we found a significant interaction between radiation exposure and cigarette smoking ($p = 0.01$). Restricting analysis to HCC cases without cirrhosis, we found a significant interaction between liver irradiation and HCV infection ($p = 0.04$). Among radiation exposed and non-exposed subjects, the odds ratios of HCC for HCV infection were 23.6 (95% C.I.: 6.57-97.34) and 3.0 (95% C.I.: 0.72-11.29), respectively. We found a significant antagonism between HBV and radiation exposure ($p = .05$), which appears to reflect the selective loss from this study of HBV-infected a-bomb survivors who died from HCC too early to be included.

#5123 THE NAD(P)H:QUINONE OXIDOREDUCTASE (NQO1) INACTIVATING C609T POLYMORPHISM IS ASSOCIATED WITH ACUTE LEUKEMIA. Y. Wang, G. Morgan, J. Wiemels, E. Kane, E. Roman, S. Rollinson, R. Cartwright, and Martyn T Smith, *Univ of CA, Berkeley, CA, and Univ of Leeds, Leeds, United Kingdom*

The causes of acute leukemia are largely unknown, although interindividual differences in multiple genetic loci are thought to influence risk of this disease. In this study we examine genetic differences in adult leukemia cases compared to matched controls in NAD(P)H:quinone oxidoreductase (NQO1), an enzyme implicated in the detoxification of quinones. A C ->T substitution polymorphism at nt 609 of the NQO1 cDNA (NQO1 C609T) results in a proline to serine substitution which is associated with a loss of NQO1 activity. This polymorphism has recently been associated with leukemias secondary to chemotherapy and also infant leukemias with *MLL* translocations, as well as being a risk factor for hematotoxicity by the leukemogen, benzene. Peripheral blood DNA samples in a population -based case-control study in England of 555 adult acute leukemia patients and 947 unaffected, age, sex, and geographically matched controls were genotyped for NQO1. The frequency of cases with low NQO1 activity (homozygous mutant + heterozygote) was significantly higher among total acute leukemia cases compared to their matched controls, odds ratio (OR) 1.32, 95% Confidence Interval (CI) 1.05–1.65. Acute lymphoblastic leukemia (ALL) cases exhibited a higher ratio